Copper(II) diacetyl-di(N^4-methylthiosemicarbazone) Cu-ATSM

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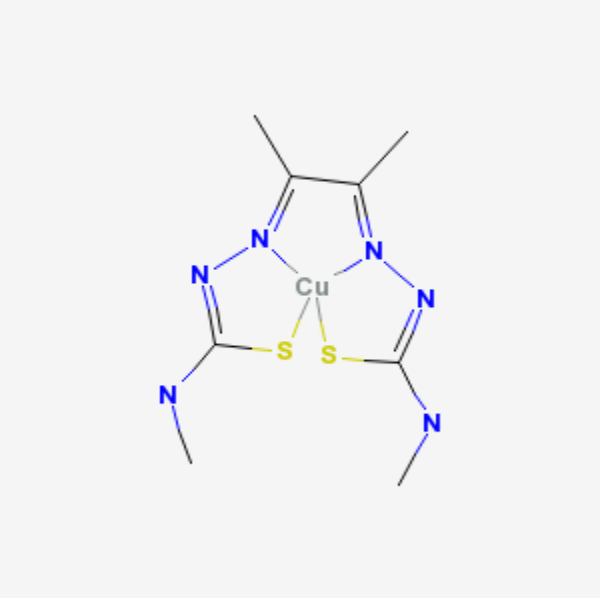
Chemical name: Copper(II) diacetyl-di(N^4-methylthiosemicarbazone)
Abbreviated name: Cu-ATSM
Synonym: Diacetyl-bis(N^4-methylthiosemicarbazone) copper(II)
Backbone: Compound
Target: Hypoxic tissue
Mechanism: Redox trapping mechanism, reduction of Cu(II) to Cu(I)
Method of detection: PET
Source of signal: $^{60,61,62,64,\ 67}$Cu
Activation: No
***In vitro* studies:** Yes
Rodent studies: Yes
Other non-primate mammal studies: Yes
Non-human primate studies: No
Human studies: Yes



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Background

[PubMed]

Hypoxia in malignant tumors can affect the outcome of anticancer treatments. Malignant tumors are relatively resistant to chemotherapy and irradiative therapy because of their lack of oxygen, which is a potent radiosensitizer. There is great interest in copper nuclides in nuclear medicine, which include isotopes with both diagnostic (^{60,61,62,64}Cu) and therapeutic (^{64,67}Cu) potential. Cu-ATSM has significant selectivity for hypoxic tissues *in vivo* and *in vitro* because of a reduction-oxidation (redox) trapping mechanism (1). Cu-ATSM accumulates avidly in hypoxic cells and delineates hypoxic areas within tumors, whereas it washes out in normoxic cells and in tissues where Cu-ATSM is not reduced and retained to the same extent (2-4).

The mechanism of retention of Cu-ATSM (with a redox potential of -297 mV) is a reduction of Cu(II) to Cu(I), followed by a loss of the radiometal from the complex. This reductive mechanism requires an intact enzymatic system of sequential electron transport chains (1, 5), which shows that the cells have an intact mitochondrial or microsomal electron transport system. Cu-ATSM accumulates mainly in the outer rims of tumor masses, which contain active tumor cells with high viability and high resistance to radiation therapy and to some chemotherapy treatments (6). For this reason, Cu-ATSM is regarded as a useful tool in positron emission tomography (PET) oncology.

Synthesis

[PubMed]

One common method for synthesizing Cu-ATSM involves buffering $CuCl_2$ in 1 M sodium acetate and then adding 15 µg of H_2ATSM (1 mg/ml of Me_2SO) and mixing for 2 min (1). The Cu-ATSM-containing solution is then washed with water, and Cu-ASTM is eluted in 0.1-ml fractions of ethanol. The radiochemical purity of the final Cu-ASTM solution is >98%.

Obata et al. (6) synthesized Cu-ATSM by mixing 4 ml of ^{64}Cu-glycine solution with 0.2 ml of ATSM solution (0.5 mmol in Me_2SO) with a radiochemical purity >99%, as determined by high-performance liquid chromatography (HPLC) on a reversed-phase column. Another method described by Petering et al. (7) uses 4-methyl-3-thiosemicarbazide and acetic acid as reagents. ^{60,61,62,64}Cu can be produced using a generator system (for ^{62}Cu) (8) or a biomedical cyclotron set up (for ^{60,61,64}Cu) in regular PET centers (3, 9).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Cu-ATSM uptake was shown to be dependent on the oxygen concentration (pO_2) by *in vitro* studies, such as those performed by Dearling et al. (4, 10) on Chinese hamster ovary cells or by Lewis et al. (4) using the 9L gliosarcoma rat model. Cu-ATSM was evaluated in the EMT6 carcinoma cell line under various degrees of hypoxia and was compared with the flow tracer Cu-PTSM and the hypoxic tracer [^{18}F]fluoromizonidazole. After 1 h, ^{64}Cu-ATSM was taken up by EMT6 cells: 90% at 0 ppm, 77% at 1 x 10^3 ppm, 38% at 5 x 10^3 ppm, 35% at 5 x 10^4 ppm, and 31% at 2 x 10^5 ppm (11).

Other studies, such as the one by Obata et al. (5) that was performed on subcellular fractions obtained from Ehrlich ascites tumor cells, clarified the retention mechanism of Cu-ATSM in tumor cells and showed that Cu-ATSM was reduced mainly in the microsome/cytosol fraction rather than in the mitochondria—a completely different process from the one occurring in normal brain cells. The reduction process in the microsome/cytosol was found to be heat sensitive and was enhanced by adding exogenous NADPH, an indication of an enzymatic reduction of Cu-ATSM in tumor cells. Among the known bioreductive enzymes, NADH-cytochrome b5 reductase and NADPH-cytochrome P450 reductase in microsomes played major roles in the reductive retention of Cu-ATSM in tumors.

Animal Studies

Rodents

[PubMed]

Cu-ATSM was shown to be dependent on the oxygen concentration, and uptake was heterogeneous in animal tumors (4). Several studies performed using rat heart models showed a selective trapping of Cu-ATSM in hypoxic tissues (3).

^{60}Cu-ATSM was used to visualize hypoxia in a heart model of an occluded, acute left anterior descending (LAD) coronary artery by *ex vivo* tissue slicing, as described by Fujibayashi et al. (12). Studies conducted using the Langendorf isolated, perfused rat model showed that specific retention of Cu-ATSM was attributable to oxygen depletion. Cu-ATSM was shown to have a rapid washout from normally perfused, isolated rat hearts, whereas in ischemic hearts, there was a 3.5-fold retention of tracer within 15 min of tracer administration.

Systemic administration of ^{64}Cu-ATSM showed a significant increase in survival time of hamsters bearing human GW39 colon cancer tumors. Radiotherapy experiments were performed in animals bearing either 7-day-old (0.5-1.0 g) or 15-day-old (1.5-2.0 g) tumors. The highest dose, 370 MBq (10 mCi) of ^{64}Cu-ATSM, increased survival to 135 days in 50% of animals bearing 7-day-old tumors, 6-fold longer than the survival of control animals (20 days), with only transient leukopenia and thrombocytopenia but no overt toxicity (13).

Other Non-Primate Mammals

[PubMed]

In studies performed on canine models of hypoxic myocardium, *Cu-ATSM PET (with *Cu defined as either ^{60}Cu, ^{61}Cu, or ^{64}Cu) showed a quantitative selective uptake in hypoxic myocardium within 20 min of tracer administration (14).

Comparative studies of intratumoral distribution by ^{64}Cu-ATSM and [^{18}F]FDG on white Japanese rabbits (6) showed a major accumulation of ^{64}Cu-ATSM around the outer rims of the tumor masses, which consisted mainly of active cells, whereas [^{18}F]FDG was mainly accumulated in the inner regions, where pre-necrotic cells exist. Those results confirmed the superiority of ^{64}Cu-ATSM for the detection of hypoxic but active tumor cell regions *in vivo*.

Non-Human Primates

[PubMed]

No reference currently available.

Human Studies

[PubMed]

Human absorbed doses were calculated from hamster biodistributions; these data showed that the dose-critical organs were the lower large intestine (1.43 ± 0.19 rad/mCi) and the upper large intestine (1.20 ± 0.38 rad/mCi). Results varied from 0.072 rad/mCi for the urinary bladder to 1.430 rad/mCi for the lower large intestine. Experimental results from tumor-bearing hamsters suggested a dose of 277,500 MBq (7,500 mCi) of ^{64}Cu-ATSM for clinical therapy trials in humans (13).

Takahashi et al. (15) performed PET with ^{62}Cu-ATSM in 6 patients with lung cancer and demonstrated high tumor uptake of the tracer in all patients, although they did not correlate such uptake with response to therapy. Other studies of ^{60}Cu-ATSM assessed by PET in patients with cervical cancer (16) and lung cancer (17) revealed clinically relevant information about tumor oxygenation that was predictive of tumor behavior and response to therapy. One of the studies was performed on 14 patients, all of whom had locally advanced cervical cancer with primary lesions >2.0 cm in diameter (1 with the International Federation of Gynecology and Obstetrics (FIGO) classification of clinical stage IB1, 1 with stage IB2, 8 with stage IIB, and 4 with stage IIIB), and the mean standardized uptake value for the primary tumors was 12.1 ± 5.5. The degree of tumor uptake of ^{60}Cu-ATSM varied from 1.2 to 12.3 (Cu-ATSM/ tumor-to-muscle activity ratio); one patient was found with no discernable uptake (2).

In their study performed on patients with head and neck cancer, Chao et al. (18) showed that a novel Cu-ATSM-guided, intensity-modulated radiation therapy (IMRT) approach could escalate radiation dose in only selective hypoxic regions within the gross target volume without compromising the advantage of normal tissue sparing of IMRT. They developed a system to accurately co-register and merge hypoxia ^{60}Cu-ATSM-PET and the therapeutic images for IMRT, with the aim of establishing a clinical-pathological correlation between ^{60}Cu-ATSM retention and radiation therapy.

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